

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Adalimumab		
Name of Active Ingredient: Adalimumab		
Title of Study: A Phase 3 Open-Label Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa – PIONEER (Open-Label Extension)		
Coordinating Investigator: Prof. Dr. med. Prof. h.c. Dr. h.c. Christos C. Zouboulis, [REDACTED] [REDACTED]		
Study Sites: 96 sites in the United States, Canada, Australia, Germany, Czech Republic, France, Switzerland, Denmark, Greece, Hungary, the Netherlands, Sweden, and Turkey		
Publications: None		
Studied Period (Years): First Subject First Visit: 12 April 2012 Last Subject Last Visit: 12 August 2016	Phase of Development: 3	
Objective: The objective of this study was to determine the long-term safety, tolerability and efficacy of adalimumab in subjects with moderate to severe hidradenitis suppurativa (HS). The pharmacokinetics and immunogenicity of adalimumab following subcutaneous (SC) injection were also to be assessed.		
Methodology: This was an open-label extension study in which all subjects received adalimumab 40 mg every week to determine the long-term safety, tolerability and efficacy of adalimumab in subjects with moderate to severe HS. Subjects who participated in Study M11-810 and Study M11-313 (who met all the inclusion criteria and none of the exclusion criteria) were eligible to enroll. The Study M12-555 Baseline (Week 0) visit and administration of the first dose of study drug in Study M12-555 was performed on the same day as the final or last visit of the prior Phase 3 study. In total, 508 subjects received study drug. The study is complete. Starting at Baseline, all subjects received open-label adalimumab 40 mg every week (ew) regardless of treatment assignment in the prior Phase 3 study. The study duration was at least 60 weeks or until marketing authorization or permanent withdrawal of the marketing application in the subject's country of residence.		

Methodology (Continued):

Hidradenitis Suppurativa Clinical Response (HiSCR), defined as at least a 50% reduction in the abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to the Baseline visit of the prior Phase 3 study, was to be determined at each study visit. If at any time on or after Week 24, a subject failed to demonstrate a clinically relevant response, the principal investigator and the subject were to evaluate the risk/benefit of having the subject continue in the study.

Study visits were to occur at Baseline, Week 4, Week 8, Week 12, Week 18, Week 24, Week 36 and every 12 weeks thereafter, at least through Week 60. Additionally, subjects who prematurely discontinued from the trial, or who completed the trial and did not initiate adalimumab therapy outside the context of the clinical trial, were to have study visits 4 and 8 weeks after the last administration of study drug to collect blood samples for the measurement of serum adalimumab concentrations and anti-adalimumab antibody (AAA).

Number of Subjects (Planned and Analyzed):

Up to 600 subjects were planned; 508 subjects were treated and analyzed.

Diagnosis and Main Criteria for Inclusion:

Subjects who participated in a prior Phase 3 study and completed the study; or achieved HiSCR at the entry of Period B, then experienced a loss of response (LOR), defined as AN count greater than the average of AN counts at Baseline and Week 12 of the prior Phase 3 study; or did not achieve HiSCR at the entry of Period B, then experienced Worsening or Absence of Improvement on or after Week 16 of the prior Phase 3 study, defined as an AN count \geq Baseline AN count at 2 consecutive visits (excluding Week 12) occurring \geq 14 days apart.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Adalimumab 40 mg/0.8 mL for SC injection

Bulk Product Lot Numbers: 10-005763, 11-003870, 11-005882, 13-000648, 13-005618, 14-002610, 15-000609, and 15-005080

Duration of Treatment:

Up to 216 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Not applicable.

Criteria for Evaluation

Efficacy:

The following efficacy measurements were determined throughout the study to evaluate the long-term efficacy of adalimumab to treat moderate to severe HS: HiSCR, abscess count, draining fistula count, non-draining fistula count, inflammatory nodule count, non-inflammatory nodule count, hypertrophic scar count, AN count, modified Sartorius score, erythema, Hurley Stage at each affected anatomic region, Patient Global Assessment of Skin Pain, Dermatology Life Quality Index (DLQI), Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP), and Treatment Satisfaction Questionnaire – Medication (TSQM).

Criteria for Evaluation (Continued)

Pharmacokinetic:

Blood samples were collected for pharmacokinetic (PK) analysis of adalimumab and analysis of AAAs were collected by venipuncture at Baseline, Week 12, Week 24, Week 36, Week 60, and at the Premature Discontinuation Visit if subject discontinued prior to Week 60.

Safety:

Safety assessments included recording of adverse events, laboratory data, physical examinations, and vital signs.

Statistical Methods

Efficacy:

The following populations were used for the efficacy analyses. Subjects must have received at least one dose of adalimumab in Study M12-555 to be included in any of the populations.

- The EW/EW/EW Population was defined as all subjects who received adalimumab 40 mg ew in both Period A and Period B of the prior Phase 3 studies. This population was used to assess the long-term safety and efficacy of ew treatment.
- The EW/EOW/EW Population was defined as all subjects who received adalimumab 40 mg ew in Period A and 40 mg every other week (eow) in Period B in the prior Phase 3 studies. This population was used to assess the safety and efficacy of dose step-up back to ew after step-down to eow in Period B of the prior studies.
- The EW/PBO/EW Population was defined as all subjects who received adalimumab 40 mg ew in Period A and placebo in Period B in the prior Phase 3 studies. This population was used to assess the safety and efficacy of retreatment with adalimumab 40 mg ew after up to 24 weeks of withdrawal in Period B of the prior studies.
- The PBO/EW/EW Population was defined as all subjects who received placebo in Period A and adalimumab 40 mg ew in Period B in Study M11-313. This population was used to assess the long-term safety and efficacy of adalimumab 40 mg ew treatment among subjects who had longer washout period (placebo treatment in Study M11-313) and did not undergo re-randomization.
- The PBO/PBO/EW Population was defined as all subjects who received placebo in both Period A and Period B in Study M11-810. This population was used to assess the safety and efficacy of 40 mg ew treatment without the initial doses of 160 mg at first administration and 80 mg 2 weeks later.

The 5 key efficacy variables were HiSCR rate, AN of 0/1/2 (among subjects with Baseline Hurley Stage II), numeric rating scale (NRS) NRS30 – at worst (at least 30% reduction and 1 unit absolute reduction in Patient's Global Assessment of Skin Pain – at worst, among subjects with baseline value ≥ 3), NRS30 – on average, and modified Sartorius score.

No formal statistical tests were conducted; descriptive statistics were provided. Continuous variables were summarized by the number of observations, mean, standard deviation, median, minimum, and maximum; discrete variables were summarized by counts and percentages with 95% confidence intervals.

Statistical Methods (Continued)

Pharmacokinetic:

Adalimumab trough serum concentrations were to be summarized by treatment group at each time point using descriptive statistics. In addition, pharmacokinetic model-based analyses were to be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

Safety:

In addition to the populations above, the following populations were used for safety analyses:

- The Continuous EW Population was defined as all subjects in the EW/EW/EW, PBO/EW/EW, and PBO/PBO/EW Populations. This population was used to analyze the safety of adalimumab 40 mg ew treatment. For subjects who dose decreased during Study M12-555, data after the first adalimumab 40 mg eow treatment was not included.
- The All Adalimumab Population was defined as all subjects who received at least one dose of adalimumab in Study M12-555. This population was used to assess the safety of adalimumab 40 mg ew with and without dose reduction to 40 mg eow.

Safety analyses included summaries (including percentages and event per 100 patient-years [E/100 PYs]) of serious adverse events (SAEs), deaths, adverse events (AEs) leading to discontinuation from the study, and AEs of special interest. Mean change in laboratory variables and vital sign variables were summarized at each visit. A listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 2 or higher and Grade 3 or higher were provided. Shift tables for changes from Baseline according to the normal range were also provided.

Summary/Conclusions

In total, 508 subjects enrolled in Study M12-555 from Study M11-810 and Study M11-313; 235 subjects (46.3%) completed the study and 273 (53.7%) discontinued. The primary reason for early discontinuation was lack of efficacy (15.0%), followed by withdrawn consent (13.2%), lost to follow-up (10.4%), and adverse event (9.1%).

Efficacy Results:

Adalimumab was efficacious in the treatment of moderate to severe HS, with persistent and clinically meaningful reduction in inflammatory lesions achieved by Week 12 (relative to the first dose of adalimumab in the prior Phase 3 study). The HiSCR rate among subjects in the EW/EW/EW Population reached 62.5% at Weeks 36 and 60 and was maintained at $\geq 56.8\%$ through Week 96 of adalimumab ew treatment. These results are supported by other efficacy endpoints, including modified Sartorius score and skin pain as measured by the Patient's Global Assessment of Skin Pain (NRS30). Among EW/EW/EW subjects who achieved at least a partial response (at least 25% reduction in abscess and inflammatory nodule count relative to baseline [AN25]) at the entry of Period B in the prior study, the proportion of subjects achieving HiSCR was 79.4% at Week 36, 68.3% at Week 60, and 65.1% at Week 96.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

To assess the impact of retreatment and dose escalation on efficacy, an analysis was performed using data across periods from subjects whose adalimumab dose was reduced from 40 mg ew in Period A to 40 mg eow in Period B in the prior Phase 3 study before dose escalating back to 40 mg ew in the current study (EW/EOW/EW Population) and from subjects who were withdrawn from adalimumab 40 mg ew therapy in Period B and restarted 40 mg ew treatment in the current study (EW/PBO/EW Population). When 40 mg ew dosing was re-introduced either after withdrawal (EW/PBO/EW Population) or 40 mg eow treatment (EW/EOW/EW Population), the HiSCR rate was gradually regained, reaching that of subjects who remained on ew treatment between Week 12 and Week 24. All populations maintained HiSCR rates above 50% at Week 96.

Pharmacokinetic Results:

Pharmacokinetic results are provided in a separate report.

Safety Results:

Safety results from the first dose of adalimumab, either in the prior Phase 3 study (Study M11-810 or Study M11-313) or in the current study (All Adalimumab Population), demonstrate the long-term safety of adalimumab in the treatment of subjects with moderate to severe HS.

No new safety risks for adalimumab were identified in Study M12-555. Adalimumab was generally well tolerated as evaluated by treatment-emergent AEs, laboratory values, and vital signs values.

Three deaths were reported during the study. One subject had multiple SAEs that included autoimmune pancreatitis, sepsis, cholangitis, septic shock, respiratory failure, and cardiac arrest. The death was considered not related to study drug by the investigator. The second subject had multiple SAEs that included pancreatic carcinoma (considered possibly related by investigator), with metastases to liver and coma hepatic (both considered not related by investigator). The third subject had an SAE of acute pulmonary oedema. The death was considered probably not related to study drug by the investigator.

In the All Adalimumab Treated Population, including data since the first dose of adalimumab (either in the initial study or in the current study), SAEs were experienced by 99 subjects (19.5%) (13.9 E/100 PYs). Twenty subjects (3.9%) had SAEs during open-label adalimumab treatment in Study M12-555 considered possibly or probably related to study drug by the investigator (pneumonia chlamydial, groin abscess, pancreatic carcinoma, pneumonia, septic shock, hidradenitis, pyoderma gangrenosum, pyelonephritis, type 2 diabetes mellitus, invasive breast carcinoma, hypertension, peritonsillar abscess, cardiac failure, infection, appendicitis, peritonitis, papillary cystadenoma lymphomatosum, pustular psoriasis, sepsis, lymphadenitis, and pneumonia viral).

Adverse events leading to study drug discontinuation were experienced by 74 subjects (14.6%) in the All Adalimumab Population. Twenty-eight subjects (5.5%) discontinued due to events of hidradenitis, and 3 (0.6%) discontinued due to events of pustular psoriasis.

Approximately two-thirds of all subjects (64.6%) experienced at least 1 treatment-emergent infection (92.0 E/100 PYs), including serious infections in 4.5% of subjects (2.4 E/100 PYs): pneumonia (3 subjects), appendicitis, cellulitis, pilonidal cyst, postoperative wound infection, sepsis, and septic shock (2 subjects each), and 1 subject each for other types of infections.

Summary/Conclusions (Continued)

Safety Results (Continued):

Treatment-emergent AEs of hidradenitis, considered to be a worsening of the underlying condition, were among the most frequently reported AEs for all treatment groups. The EW/EW/EW group experienced the lowest proportion of events (23.7 E/100 PYs) and the EW/PBO/EW group had the highest proportion of events (36.4 E/100 PYs).

Ten subjects reported one or more events of the following malignancies: breast cancer stage III, pancreatic carcinoma, metastases to liver, Hodgkin's disease, seminoma, basal cell carcinoma, invasive breast carcinoma, keratoacanthoma, and squamous cell carcinoma of skin. Excluding lymphoma, hepatosplenic T-cell lymphoma, leukemia, non-melanoma skin cancer or melanoma, the malignancy rate was 0.6 E/100 PYs.

No new opportunistic infections were reported. There were no cases of tuberculosis activation reported. Thirteen cases of latent tuberculosis were reported, all of which were asymptomatic and 3 of which led to discontinuation of study drug. Worsening or new onset of psoriasis was reported in 28 (5.5%) of subjects (3.0 E/100 PYs). One event of pustular psoriasis was serious and 7 events resulted in discontinuation of study drug: pustular psoriasis (3 subjects), psoriasis (2 subjects), dermatitis psoriasiform (1 subject), and guttate psoriasis (1 subject).

No clinically meaningful trends were observed in laboratory assessments and vital sign measures.

Seven pregnancies have been reported in this study. One subject had a first trimester spontaneous abortion, 5 subjects gave birth to live infants with no medically significant complications or birth defects noted, and 1 subject was lost to follow-up.

To assess the impact of retreatment and dose escalation on the safety profile, data were analyzed from the first dose of adalimumab in Study M12-555 among subjects in the EW/EOW/EW Population and EW/PBO/EW Population, respectively. Re-introduction of adalimumab after withdrawal and dose increase following a period of dose reduction were not associated with an increase in AEs.

Overall, the safety profile of adalimumab treatment observed in this study is expected given the population of moderate to severe HS.

Conclusions:

Results from this final analysis support the long-term safety and efficacy in the treatment of adults with moderate to severe HS. The efficacy of adalimumab 40 mg ew therapy was demonstrated in the treatment of abscesses, inflammatory nodules, and reduction of skin pain. No new safety risks for adalimumab were identified in this study.